

9. Halazone tablets over 12.5 per cent. to under 25 per cent. of the professed content were found.

10. Chloramine-T and Halazone are sufficiently stable to be kept over a period of five years. Dichloramine-T, on the other hand, decomposes slowly.

CHICAGO, ILLINOIS

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## SYNTHETIC HYPNOTICS IN THE BARBITURIC ACID SERIES.

BY ARTHUR W. DOX.

The increasing demand for sleep-producing drugs is perhaps one of the characteristics of the restless age in which we now live. Not a year passes but half a dozen new synthetic hypnotics appear in the patent literature and a few of these find their way into the drug market. Most of these fail to meet the claims made by the manufacturers and are soon discarded, and the physicians continue to prescribe the eight or ten more or less familiar drugs that have survived several decades of clinical experience. Meanwhile, the chemical and pharmaceutical laboratories continue their search for the ideal hypnotic, for it must be admitted that none of the hypnotics in present-day use are entirely free from certain objectionable qualities.

Long before our era of chemical and pharmaceutical research the sleep-producing properties of opium and alcohol were widely known. In oriental countries hashish, or *cannabis indica*, has been used for centuries, but this has never become popular in our western civilization. Among the natural drugs, *hyocyamus* is perhaps the only other hypnotic of any importance. The first three, opium, alcohol and *cannabis*, are decidedly habit-forming. As a matter of fact, only a very small percentage of the total consumption of these drugs can be considered legitimate in the sense of being used under circumstances where a physician would feel justified in prescribing them.

Opium, including its chief constituent, morphine and the morphine derivatives—codeine, heroine, etc.—has been both a blessing and a curse to humanity. For the relief of acute pain, especially in post-operative surgery, no satisfactory substitute has yet been discovered. On the other hand, the morphine habit has fastened itself upon thousands of otherwise useful citizens and left them physical and moral wrecks. The discovery of synthetic hypnotics which are now used in a great many cases where morphine was formerly prescribed, represents, therefore, a distinct advance in medical science. It may be said in general that for the relief of insomnia or sleeplessness due to other causes than acute pain, the use of morphine or its derivatives is no longer necessary.

Curiously enough, none of the synthetic hypnotics bears the slightest chemical resemblance to morphine. The exact structure of the morphine molecule is still unknown, but we know that it is far more complex than any synthetic hypnotic thus far used. The presence of a phenanthrene nucleus, an oxygen bridge forming a furane ring, two hydroxyls one of which is phenolic and the other alcoholic, and a nitrogen ring bearing a methyl group, is about all that has been definitely proved of the morphine structure. On the other hand, some of our common sleep-producing drugs are extremely simple and easily synthesized. The difference is not so much in the size as in the compactness of the molecule. For example, morphine has a molecular weight of 285, and luminal, one of the most powerful of our synthetic

hypnotics, a molecular weight of 232; yet morphine contains five cyclic nuclei and luminal only two.

The great advantage of the synthetic hypnotics over morphine is in their lack of injurious effect upon the higher brain centers and in the fact that they are not habit-forming in the ordinary sense. Individuals are occasionally met with who rely to an unnecessary extent upon these drugs, but the habit, if it can be called such, is hardly a physiological craving. For that matter, any drug may be considered habit-forming. Self-medication is one of our favorite pastimes. We have only to call to mind the number of people among our own acquaintance who resort to a dose of aspirin upon every possible pretext. With the exception perhaps of chloral hydrate the ordinary sleep-producing drugs only rarely develop an injurious habit. The reason is probably their lack of effect upon the higher brain centers and their failure to produce sensations of exhilaration or mental exaltation.

In briefly reviewing the history of synthetic hypnotics, we find that chloral hydrate,  $\text{CCl}_3\text{CH}(\text{OH})_2$ , was the first to be introduced into medicine. Like many others, this substance was known to chemists years before its medicinal properties were discovered. Liebig prepared and described chloral hydrate in 1832 but it was not until 1869 that Liebreich found it to be a hypnotic and in 1874 it was introduced into the British Pharmacopœia. The search for other hypnotics then began. Only those which may be regarded as distinct types and which have come into extensive use will be alluded to in this brief discussion. Paraldehyde,  $(\text{CH}_3\text{CHO})_3$  made its appearance in 1883; urethane,  $\text{C}_2\text{H}_5\text{OCONH}_2$ , in 1885; hypnone,  $\text{C}_6\text{H}_5\text{-COCH}_3$ , in 1886; amylene hydrate,  $(\text{CH}_3)_2\text{C}_2\text{H}_5\text{COH}$ , in 1887; sulfonal,  $(\text{CH}_3)_2\text{C}(\text{SO}_2\text{C}_2\text{H}_5)_2$  in 1888; chloretone,  $\text{CCl}_3(\text{CH}_3)_2\text{COH}$ , in 1899; and veronal,  $(\text{C}_2\text{H}_5)_2\text{C}(\text{CONH})_2\text{CO}$ , in 1903.

Analogs and homologs of these in which, for example, bromine is substituted for chlorine, or ethyl for methyl, and condensation products with other substances, have made their appearance in great numbers. Many are patented and sold under fantastic names. In practically all cases their therapeutic action is due to a chemical structure represented by one or more of the substances listed above.

As already stated, the ideal hypnotic has not yet been found. Chloral hydrate is regarded by many physicians as habit-forming, and it has a decidedly depressant action on the heart. Urethane, hypnone and paraldehyde are effective only in comparatively large doses and have a disagreeable nauseating taste. Paraldehyde is widely used in hospitals, but is so unpleasant to take that few physicians would risk losing their practice by administering it to private patients. Sulfonal, as well as its homolog, trional, has a tendency to destroy the blood corpuscles. Chloretone and veronal are perhaps the most satisfactory, yet in doses sufficient to produce quick results their action is too prolonged. The ideal hypnotic should have a high "factor of safety," that is, a wide range between effective dose and toxic dose, and thus minimize the danger of over dosage. It should be prompt in its action and free from after effects. It should not interfere with circulation or respiration. And lastly, it should be non-habit forming and at the same time free from disagreeable taste or odor.

Now what is the mode of action of these drugs? Many theories have been proposed but not one of them is entirely satisfactory. As has been stated, they

are unlike morphine in that they do not affect the higher brain centers, their action being probably limited to the central nervous system and the medulla. The most ingenious explanation is known as the Overton-Meyer theory of narcosis. According to this theory the action of synthetic hypnotics is mechanical rather than chemical. Overton found that the effectiveness of these drugs is proportional to their "distribution coefficient," that is, the ratio of their solubility in fats and lipoids to their solubility in water. Nerve tissue is composed largely of fats and lipoids, hence there would tend to be an accumulation in the nerve tissue of such drugs as are more soluble in lipoids than in water. The nervous system thus becomes partially saturated with a foreign substance and its functioning is mechanically retarded. In support of this theory we have the fact that animals in an emaciated condition, in other words, with less adipose tissue to absorb the drug, are more susceptible to hypnotics, also the fact that certain hypnotics, for example veronal, undergo practically no change in the body and are finally excreted unchanged. On the other hand, many substances in the aromatic series for which hypnotic properties might be predicted from their distribution coefficients, have no such action. Possibly, as Traube suggests, surface tension may also be an important factor. Fuchs has pointed out that all of the hypnotics with the exception of the sulfones contain a hydroxyl group, or a carbonyl group capable of tautomerizing to a hydroxyl. The sulfones are the most readily destroyed in the body and their apparent exception may be ruled out on the assumption that a transition product containing a hydroxyl is formed from them. It must be admitted, nevertheless that the action of hypnotic drugs is still as much a mystery as the phenomenon of natural sleep.

A discussion of the various types of hypnotics and their chief representatives would be far beyond the scope of this paper. We shall limit ourselves therefore to the newest type, the veronal series, in which the writer has been conducting investigations during the past three years.

Veronal, also known as Barbital, was introduced into medicine by Fischer and Mering in 1903. It is 5,5-diethylbarbituric acid,  $(C_2H_5)_2C(CONH)_2CO$ . This substance, like chloral hydrate, was known to chemists long before its physiological action was discovered. It was first prepared by Conrad and Guthzeit in 1882 by the action of ethyl iodide on the silver salt of barbituric acid. For twenty years no further attention was paid to it. Then came the announcement by Fischer and Mering of the remarkable sleep-producing properties of this substance, and a description by Fischer and Dilthey of a far more satisfactory and economical method of preparing it. Various processes for the manufacture of veronal have been patented, but the method originally described by Fischer and Dilthey—the condensation of ethyl diethylmalonate with urea in the presence of sodium ethylate—is the only one that has been successful on a commercial scale.

Like all of Emil Fischer's work this investigation was painstaking and thorough. He prepared a number of homologs of veronal, among which may be mentioned dimethyl, methyl-ethyl, methylpropyl, dipropyl, ethylpropyl, diisobutyl, diisoamyl and dibenzyl-barbituric acids. With increasing size of these alkyl groups the hypnotic effect increases up to a certain point, then decreases. As might be expected, the two extremes, dimethyl and diisoamyl, have very little action, and the intermediate derivatives follow a parabolic curve with dipropyl at the peak.

Diethylbarbituric acid with further substitution on the nitrogen, as for example, 5,5-diethyl-1-methylbarbituric acid was found to be toxic. Replacement of the oxygen in the 2-position by sulphur, as in 5,5-diethyl-2-thiobarbituric acid gave a toxic product, whereas a similar replacement by the imino group, NH, as in diethylmalonylguanidine, gave an inert substance. All of these products, it will be noted carry two alkyl groups on the 5-carbon atom of the pyrimidine nucleus. If only one alkyl is present as in monoethyl or monopropyl-barbituric acid hypnotic action is absent. This is also the case when the barbituric acid ring is opened up, as for example, the ureide of diethylmalonic acid.

The dialkylbarbituric acids which has been almost entirely neglected during the twenty years preceding Fischer's patent now became the subject of feverish research activity particularly in the German laboratories. Patent after patent appeared in rapid succession, mainly of processes for the manufacture of veronal. Most of these processes are roundabout methods of synthesis and could not possibly compete with Fischer's method on a commercial scale.

Among the other dialkylbarbituric acids of therapeutic value for which specific patents have been granted may be mentioned phenylethyl, cyclohexylethyl, diallyl, phenylallyl, dibutyl and isopropylethyl-barbituric acids. Phenylethylbarbituric acid, sold under the names "luminal" and "phenobarbital" is by far the most important of these. It is said to be two and one-half times as powerful as veronal, and is used extensively in the treatment of epilepsy. Whereas the hypnotic effect of veronal is sometimes preceded by a brief period of excitement, luminal manifests its sedative action almost immediately, and for that reason is often used in the treatment of violent cases of insanity and to ward off epileptic seizures. Of the other derivatives just mentioned, the diallyl is about the only one which can be obtained in the market. It is sold under the name "dial." It is undoubtedly a good hypnotic, but the Council of Pharmacy and Chemistry of the American Medical Association has refused to accept it for "New and Non-Official Remedies" because of an overstatement of the manufacturer's claims. The most recent derivative is perhaps isopropylallyl-barbituric acid, known as "allonal." At the present writing, one of our large pharmaceutical houses is about to put isoamylethylbarbituric acid on the market. A discussion of these new derivatives is out of the question because very few data are available except the advertising propaganda. As regards cost of manufacture, none of these derivatives can compete with veronal, especially those containing two different alkyl groups. Superior merits or special uses must be demonstrated if the product is to be a commercial success. This was actually done in the case of luminal, which however, is not a competitor of veronal, but a distinct drug used for special purposes. Butylethylbarbituric acid is on the European market under the name "someryl." It was prepared and described by the writer several weeks before Carnot and Tiffeneau published their description of it. Since the cost of manufacture by any conceivable process would be greater than that of veronal and its action is not essentially different, we did not consider it worth while to apply for a patent.

The study of many other drugs has shown that the physiological action is often due to some particular grouping of atoms in the molecule. A classic example is the synthesis of the local anesthetic procaine based upon a study of the chemical structure of the alkaloid cocaine. Here it was found that the essential groupings

are the benzoyl radical and a tertiary amine. A much simpler derivative containing these two groupings was then prepared and found to be an excellent substitute for cocaine without the habit forming tendencies. Similarly, the ideal hypnotic may eventually be synthesized when we understand fully the structure of the morphine molecule. For the present, however, we are interested in determining the essential grouping to which veronal owes its hypnotic action. First of all, what grouping has it in common with other known hypnotics? Phenylethyl-hydantoin, diethylbromacetylurea, diethylhomophthalimide and phenylethyldiketotetrahydroxazole have, in common with veronal, the grouping  $CR_2-CO-NH-CO$ . It is not unlikely that this grouping is a "hypnophore," to coin a word analogous to the familiar "chromophore" of the dye chemist. The alkyl groups ( $R_2$ ) may of course be varied within a limited range.

One of the alkyls may be a cyclic structure, *e. g.*, phenyl or cyclohexyl, but thus far the other alkyl has invariably been an open chain. Now how would the physiological properties of these dialkylbarbituric acids be affected if the two alkyls were linked together into a cyclic structure? The molecule would then consist of two cyclic nuclei with a single carbon atom common to both; in other words, a *spiro* derivative, a type of compounds of which comparatively few representatives are known. The writer, in collaboration with Lester Yoder, succeeded in preparing several such compounds. The spiro derivative trimethylenebarbituric acid corresponds to methylethylbarbituric acid in which the methyl and ethyl groups are closed into a four-membered ring. Similarly, pentamethylenebarbituric acid corresponds to ethylpropylbarbituric acid with the terminal carbons of the ethyl and propyl groups united into a six-membered ring. To our amazement, both of these derivatives were entirely devoid of hypnotic action. Likewise, the alkylidenebarbituric acids, with a single alkyl group linked to the 5-carbon of the pyrimidine ring through a double bond, as benzylidene-barbituric acid,  $C_6H_5CH=C(CONH)_2CO$ , are inactive.

We then undertook to vary the urea grouping of the barbituric acid derivatives. By condensing dialkylmalonic esters with amidines instead of urea we obtained a very interesting series of pyrimidines in which the  $-NH-CO-NH-$  grouping of the veronal series was replaced by  $-NH-CR=N-$ . These also were devoid of hypnotic action. Evidently then the "hypnophore" group referred to above is actually the essential part of the molecule. Even so slight an alteration of the urea grouping as the reduction of the carbonyl to a methylene had been found by Einhorn to destroy the hypnotic properties of veronal.

Another series of dialkylbarbituric acids which we prepared represents the veronal series with a benzyl group in place of one of the ethyls. Since the comparatively recent introduction of benzyl derivatives into medicine as antispasmodics, it occurred to us that the substitution of a benzyl for an ethyl in veronal might give us a derivative with both hypnotic and anti-spasmodic properties. Benzylethylbarbituric acid and a number of its homologs were accordingly prepared. The most active member of the series was the benzylethyl derivative itself. As we anticipated, it was a powerful hypnotic, but contrary to our expectations, instead of being an antispasmodic it was quite the reverse. The narcosis produced in the experimental animals was preceded by tetanic convulsions. Since the publication of this work, our results have been confirmed by Shonle and Moment of

Indianapolis. These startling results led us to a more critical examination of Macht's deductions regarding benzyl therapy. We are now convinced that the supposed "specific benzyl effect" claimed by Macht is simply a higher alcohol effect. With the benzyl attached directly to carbon as in our derivative a hydrolysis into benzyl alcohol is extremely unlikely, whereas in benzyl benzoate and other benzyl esters such hydrolysis readily occurs. On the basis of chemical structure our derivative, with the benzyl attached directly to the carbon of a cyclic nucleus, resembles the alkaloid papaverine, on which Macht based his deductions, more closely than do his benzyl esters. At present we see no possibility of utilizing benzylethylbarbituric acid therapeutically.

Of the various preparations on the market containing dialkylbarbituric acids only those representing salts with bases can be considered chemical compounds. The sodium salt of veronal, for example, appears under the name "medinal." It has the advantage of greater solubility and for that reason can be used hypodermically, but its action is no different from that of veronal. Salts with alkaloids can also be procured, and in these preparations the veronal and the alkaloid exert their specific actions independently. Other preparations, despite the manufacturer's claims to the contrary, are mere mixtures and not chemical combinations. We considered it of interest therefore to determine the effect of combining a dialkylbarbituric acid in a stable union with other substances of known physiological activity. The products represent ethylpropyl- and isoamylpropyl-barbituric acids united through the gamma carbon of the propyl group to diethylamine, ethylaniline, acetanilide and phenacetin, respectively. Acetanilide and phenacetin, for example, are antipyretics and ethylpropylbarbituric acid a strong hypnotic. Preliminary tests showed that mixtures in molecular proportions retained at least the hypnotic action of the barbituric acid. It remained to be determined what the effect would be of uniting the two constituents in a stable union. The synthesis of a typical preparation involved the following steps: Ethyl malonate  $\rightarrow$  ethyl ethylmalonate  $\rightarrow$  ethyl ethylbromopropyl-malonate  $\rightarrow$  ethyl ethylacetphenetidino-propyl-malonate  $\rightarrow$  ethylacetphenetidino-propylbarbituric acid. The final product may be represented by the formula  $C_2H_5O.C_6H_4N(COCH_3)CH_2CH_2CH_2(C_2H_5)-C(CONH)_2CO$ . The substance proved to be so stable that even the acetyl group was very difficult to remove by boiling with strong acid or alkali. Animal tests showed that the hypnotic properties of the barbituric acid had disappeared entirely. This we attribute to the insolubility of the substance which prevents absorption and to its great stability which interferes with the liberation of a simple dialkylbarbituric acid by hydrolysis. On the other hand, the corresponding derivative with diethylamine in place of phenacetin was soluble in water but less soluble in organic solvents thus reversing the distribution coefficient required by the Overton-Meyer theory. We believe that in these derivatives a molecular magnitude has been reached considerably beyond that encountered in the ordinary synthetic hypnotics or in morphine itself, without however, acquiring the compactness of the alkaloid molecule.

It will be noted from the foregoing discussion that luminal (phenylethylbarbituric acid) is the only simple disubstituted barbituric acid containing an aromatic radical linked directly to the pyrimidine nucleus. We found that ethylphenoxybarbituric acid, which is luminal with an oxygen inserted between the phenyl

group and the pyrimidine ring was not a hypnotic. Evidently the phenyl must be attached directly to carbon. The question now arises whether the introduction of a second phenyl would increase the physiological activity still further. A search through the literature showed that no attempts have been recorded to prepare such derivatives. The simplest of this type would be 5,5-diphenyl-barbituric acid, *i. e.*, veronal with both ethyls replaced by phenyls. An isomer of this has been described, *viz.*, 1,3-diphenylbarbituric acid, but here both of the phenyls are attached to nitrogen instead of carbon and the substance therefore does not belong to the veronal series. Our attempts to prepare 5,5-diphenylbarbituric acid were unsuccessful owing to the instability of ethyl diphenylmalonate which was used in the final step of the synthesis. We did however, prepare a substituted derivative, namely, di-(*p*-hydroxyphenyl)-barbituric acid,  $(\text{HO}\text{C}_6\text{H}_4)_2\text{C}(\text{CONH})_2\text{CO}$ , also its isomer diphenoxybarbituric acid,  $(\text{C}_6\text{H}_5\text{O})_2\text{C}(\text{CONH})_2\text{CO}$ . Neither of these substances showed physiological activity.

An examination of the structure of the synthetic hypnotics commonly used shows that practically all are aliphatic derivatives. Where an aromatic grouping is present, as in luminal and phenylethylhydantoin, the aromatic group comprises a relatively small part of the molecule. On the other hand, aromatic derivatives for which hypnotic properties might be predicted on the basis of their distribution coefficient and molecular stability are generally inert.

Hypnone (acetophenone) perhaps comes the nearest to being an aromatic hypnotic, but a further increase in the aromatic groupings, as in benzophenone and benzhydrol, causes the hypnotic action to disappear. It is of interest to note that the two barbituric acids under discussion consist essentially of two benzene rings and one pyrimidine ring, that is, they are preponderantly aromatic. The hydantoins furnish a parallel case; phenylethylhydantoin, mainly aliphatic, is a hypnotic, while diphenylhydantoin, mainly aromatic, is not. Further evidence is of course required to establish this point, but from the data at hand it would appear that a search for hypnotics among derivatives that are essentially aromatic is not very promising.

Experimental hypnotics must of course be thoroughly tested out with animals before even preliminary tests are made with human subjects. Various animals have been used for this purpose. Fischer and Mering's original experiments with veronal and its homologs were performed with dogs. The more active hypnotics when administered orally in a one gram dose to a dog of average weight cause first a marked muscular incoördination followed by drowsiness and finally sleep which lasts six or eight hours. We found in our experiments that preliminary tests could be performed very satisfactorily with white mice by intraperitoneal injections of either an aqueous solution of the sodium salt or an olive oil solution of the free acid. The advantages of this method are the smaller amount of material required for the test, a great saving of laboratory space and the avoidance of certain disagreeable features always met with in experimentation with larger animals. For example, the effective dose of veronal for a 20-gram mouse is only 0.006 Gm. Within twenty minutes the mouse is in a state of coma which lasts for several hours, after which recovery takes place without any apparent after-effects. This method we have found very useful as a preliminary test to eliminate from further consideration derivatives which are physiologically inert.

From our study thus far of the barbituric acids certain negative data are presented for the purpose of narrowing down the scope of future investigation. The following tentative conclusions may be drawn, supplementary to those of Fischer and Mering.

1. To manifest hypnotic action without undesirable after-effects, the two alkyl groups in the 5-position of the pyrimidine ring should have a total number of carbon atoms not less than four or more than eight.
2. At least one of the alkyl groups must be in the form of an open chain.
3. The benzyl group is undesirable because of its tendency to cause convulsions.
4. The urea grouping  $\text{—NH—CO—NH—}$  may not be replaced by the amidine grouping  $\text{—NH—CR=NH—}$ .
5. Increase in the size of the molecule beyond, say, a molecular weight of 250 results in loss of hypnotic activity.
6. Not more than one of the two alkyl groups should be aromatic in character.
7. We believe that the hypnophore group in the veronal series is  $\text{—CR}_2\text{—CO—NH—CO—}$ .

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*U. S. Patents on Dialkylbarbituric Acids.*

Diethyl	782,739 (1905)	veronal	Phenylallyl	1,056,793 (1913)
Phenylmethyl	1,025,526 (1912)		Isopropylethyl	1,255,951 (1918)
Phenylethyl	1,025,872 (1912)	luminal	Dibutyl	1,331,712 (1920)
Diallyl	1,042,265 (1912)	dial	Isopropylallyl	1,444,802 (1923) allonal

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 PAPER No. 20.

## THE HYDROGEN ION CONCENTRATION OF SOME U. S. P. PRODUCTS.

### SHOULD LITMUS BE SUPPLEMENTED BY MORE SENSITIVE INDICATORS?

BY PETER MASUCCI AND MARGARET I. MOFFAT.

The hydrogen ion concentration of certain U. S. P. products was determined electrometrically by means of a hydrogen electrode. These measurements were made on routine samples which were submitted to the Analytical Laboratory to be tested for identity and purity. The solutions of each substance was made